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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/676,725
Filing Date: October 01, 2003
Appellant(s): ROSENBLUM, MICHAEL G.

David L. Parker
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 11, 2008 appealing from the Office action mailed April 28, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

4,590,071	Scannon et al	5-1986
4,771,128	Ferris et al	9-1988
4,753,894	Frankel et al	6-1988

4,666,845 Mattes et al 5-1987

Kirkwood et al. "Scintigraphic detection of metastatic melanoma using indium 111/DTPA conjugated anti-gp240 antibody (ZME-018)" J of Clinical Oncology, Vol. 5, no. 8 (1987), pp. 1247-1255.

Blick et al. “Phase I study of recombinant tumor necrosis factor in cancer patients” Cancer Research, Vol. 47 (1987), pp. 2986-2989.

Ghose et al. “The design of cytotoxic-agent-antibody conjugates” Critical Reviews Therapeutic Drug Carrier Systems, Vol. 3, issue 4 (1987), pp. 263-359.

Ashcroft et al. “Fullerene (C_{60}) immunoconjugates: interaction of water-soluble C_{60} derivatives with the murine anti-gp240 melanoma antibody” Chem Commun, (2006), pp. 3004-3006.

Ferrone et al. “Human high molecular weight-melanoma associated antigen as a target for active specific immunotherapy” J of Dermatology, Vol. 15 (1988), pp. 457-465.

Martin et al. “Retroviral vector targeting to melanoma cells by single-chain antibody incorporation in envelop” Human gene Therapy, Vol. 9 (1998), pp. 737-746.

Oratz et al. "Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (X-MMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: results of a phase II trial" J Biological Response Modifiers, Vol. 9 (1990), pp. 345-354.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(A) **Claims 7, 10, 13, 14, 21, 24-29, and 32 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as evidenced by Kirkwood et al (J of Clinical Oncology, 1987, 5:1247-1255, IDS).

Scannon et al teach a method of treating melanoma in humans comprising administering an antibody-ricin A toxin conjugate, wherein the antibody of the conjugate binds the melanoma-specific antigen of 240kD and is a monoclonal antibody (abstract; col. 5, lines 27-60; col. 7, lines 30-50; Table II). Scannon et al teach that the 240kD antigen is specifically expressed in melanoma, hence the antigen would be a cell surface antigenic marker at a concentration in excess of that found at non-target sites (col. 6, lines 21-27). The human patient treated with the antibody conjugate specific for melanoma would necessarily have been identified or diagnosed as a patient having a melanoma tumor and the patient's melanoma would be expressing the melanoma-

specific antigen targeted by the antibody conjugate for killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered. Scannon et al teach that the antibody-toxin conjugate allows for specific targeting of toxins to melanoma for human melanoma therapy because of selective binding activity of the antibody for the melanoma-specific antigen (col. 1, lines 55-68).

As evidence by Kirkwood et al, the XME-018 antibody binds to gp240, a 240kD melanoma-associated antigen that has exhibited greater restriction to melanoma than other antigens (p. 1247). Scannon et al does not teach that the 240kD antigen is gp240, however, the claimed antigen appears to be the same as the prior art cell surface antigen that ZME-018 antibody recognizes, hence Scannon et al teach that an antibody of the antibody-conjugate that binds the same antigen recognized by antibody ZME-018. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Scannon et al does not teach that the antibody is conjugated to a biological response modifier and that the modifier is TNF.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to

toxic drugs such as ricin A toxin and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the ricin A toxin of the antibody conjugate taught by Scannon et al because Ferris et al teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Scannon et al in order to selectively kill melanoma cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat melanoma in a human patient because the antibody taught by Scannon et al successfully and specifically targets a toxin to human melanoma cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody- ricin A toxin conjugate taught by Scannon et al had a known function for treating melanoma by targeting the toxin to melanoma that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris et al is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the ricin toxin), and the results of the substitution would have been predictable for treatment.

(B) **Claim 16 remains rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of Blick et al (Cancer Research, 1987, 47:2986-2989).

Scannon et al and Ferris et al teach a method of treating melanoma in a human comprising identifying a patient having melanoma, of which the melanoma express a cell surface antigen found in excess of that found at other non-target sites, obtaining and administering an antibody-TNF conjugate wherein the antibody binds the melanoma antigen and allows for specific delivery of the TNF to melanoma cells as set forth above.

Scannon et al and Ferris et al do not teach that the TNF is TNF-alpha.

Blick et al teach a method of treating cancer in a human patient with TNF-alpha with evidence of antitumor effects for some patients (p. 2988, col. 1; p. 2989, col. 1). It is well known in the art and the reference teaches that cytokines are known to have cytostatic and cytotoxic effects against a wide range of human tumor cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use TNF-alpha taught by Blick et al as the TNF conjugated to the antibody taught by Scannon et al and Ferris et al because TNF-alpha is a well known biological response modifier that has antitumor activity and is a natural defense against tumors produced by activated macrophages. One would have been motivated to use the TNF-alpha as the TNF of the antibody conjugate in order to

specifically kill tumor cells. One would have a reasonable expectation of success treating melanoma using an antibody-TNF-alpha conjugate because of its known antitumor effects.

Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF-alpha for the TNF), and the results of the substitution would have been predictable.

(C) **Claim 23 remains rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of Ghose et al (Crit Rev Ther Drug Carrier Syst, 1987, 3:263-359).

Scannon et al and Ferris et al teach a method of treating melanoma in a human comprising identifying a patient having melanoma, of which the melanoma express a cell surface antigen found in excess of that found at other non-target sites, obtaining and administering an antibody-TNF conjugate wherein the antibody binds the melanoma antigen and allows for specific delivery of the TNF to melanoma cells as set forth above. Ferris et al further teach the recombinant production of TNF (Example 3, col. 6).

Scannon et al and Ferris et al do not teach that the antibody is fused to the biological response modifier (or TNF).

Ghose et al teach recombinant technology to create hybrid antibody molecules that are directed against the tumor-associated antigen and linked to biological products with antitumor activity such as tumor necrosis factor (p. 334). Ghose et al also teach the advantage of a fused molecule over a conjugated molecule because fused molecules produced from transfection methods are more likely to be free of contaminating oncogenic viruses and nucleic acids as opposed to monoclonal antibodies produced by malignant cells used for conjugation to a biological response modifier (p. 334). Ghose et al teach the advantage of a fused molecule as a "tailored antibody molecule" (p. 334) wherein genetic engineering can create one molecule to both target and treat a cancer cell.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an antibody fused to a biological response modifier as taught by Ghose et al into the method of Scannon et al and Ferris et al in order to make a fused "tailored" immunoconjugate free of contaminants for treating cancer. One would have been motivated to incorporate an antibody fused to a biological response modifier into the method taught by Scannon et al and Ferris et al because Ghose et al teach the advantages of being able to tailor a fused molecule to comprise the desired target antibody and biological response modifier, and the production of fused molecules resulting in less contamination, a factor important in the manufacture of drugs for treating cancer in human patients. One would have a reasonable expectation of success using a fused antibody-biological response modifier molecule in the method

taught by Scannon et al and Ferris et al because the fused antibody molecule serves the same function as the conjugated antibody molecule.

Given the known technology for making recombinant or fused antibodies, and given the known functions of the antibody and biological response modifier, one of skill in the art could have substituted one known element for another (the fused antibody for the conjugated antibody), and the results of the substitution would have been predictable for cancer treatment.

(D) **Claims 7, 24, 26-29, and 30 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,753,894, Frankel et al, filed 1/11/1985, issued 6/28/1988 in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988.

Frankel et al teach a method of treating breast cancer in a human comprising administering an antibody-ricin A toxin conjugate wherein the antibody binds a breast cancer antigen that is a cell surface antigen expressed at higher concentrations on the breast cancer compared to that found on normal tissue, non-target sites, and wherein the antibody is monoclonal (abstract; col. 3, line 16 through col. 5, line 52; Tables 1 and 2; col. 14, line 50 through col. 15, line 10; Table 6). The patient treated with the antibody conjugate specific for breast cancer would necessarily have been identified or diagnosed as a patient having a breast tumor and the patient's breast cancer would be expressing the breast cancer-specific antigen targeted by the antibody conjugate for

killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered.

Frankel et al does not teach that the antibody is conjugated to a biological response modifier.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the ricin A toxin of the antibody conjugate taught by Frankel et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Frankel et al in order to selectively kill breast cancer cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat breast cancer in a human patient because the antibody taught by Frankel et al successfully and specifically targets a toxin to human breast cancer cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody- ricin toxin conjugate taught by Frankel et al had a known function for treating breast cancer by targeting the toxin to breast cancer cells that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the ricin A toxin), and the results of the substitution would have been predictable for cancer treatment.

(E) **Claims 7, 24, 26-29, 31 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent 4,666,845, Mattes et al, filed 12/16/1983, issued 5/19/1987, in view of US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988.

Mattes et al teach a method for treating cervical carcinoma in a human comprising administering a monoclonal antibody, MH94, conjugated to a toxin to kill cancer cells (col. 14, lines 27-40). Mattes et al teach that monoclonal antibody MH94 binds to an antigen found on human cervical carcinoma cells at concentrations in excess of that found in other tissues (Table I, Table II, col. 4, lines 15-15; col. 11, line 55 through col. 12, line 18; col. 13, lines 1-11). Mattes et al teach methods of diagnosis using the monoclonal antibody tagged with a radioactive label for localizing cervical carcinoma in a patient (col. 14, lines 19-26). The patient treated with the antibody

conjugate specific for cervical carcinoma would necessarily have been identified or diagnosed as a patient having a cervical carcinoma and the patient's cervical carcinoma would be expressing the cervical carcinoma -specific antigen targeted by the antibody conjugate administered for killing tumor cells. An antibody conjugate composition is obtained because it had to be obtained in order to be administered.

Mattes et al does not teach that the antibody is conjugated to a biological response modifier.

Ferris et al teach how to make an antibody conjugated to the biological response modifier TNF (Example 3, col. 6). Ferris et al teach that by conjugating antibodies to toxic drugs such as ricin A toxin and TNF, the affinity of the drugs for particularly types of tumor cells is increased and the drugs can then exert their effects selectively, by virtue of the specific antibody carriers, against those cells (col. 1, lines 14-62; col. 2, lines 53-65). Ferris et al teach that methods of preparing immunoconjugates are known in the art (col. 3, lines 17-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made substitute TNF for the toxin of the antibody conjugate taught by Mattes et al because Ferris teach that antibodies conjugated to TNF will selectively kill tumor cells targeted by the antibody. One would have been motivated to use an antibody-TNF conjugate in the method of Mattes et al in order to selectively kill cervical carcinoma cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat cervical carcinoma

in a human patient because the antibody taught by Mattes et al targets a toxin to human cervical carcinoma cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody-toxin conjugate taught by Mattes et al has a known function for treating cervical carcinoma by targeting the toxin to cervical carcinoma cells that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the toxin), and the results of the substitution would have been predictable for cancer treatment.

(10) Response to Argument

(A) With regards to claims 7, 10, 13, 14, 21, 24-29, and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, **Scannon et al**, in view of US Patent 4,771,128, **Ferris et al**, as **evidenced by Kirkwood et al**, Appellant argues a person of skill in the art at the time of filing would not be motivated to combine the references with a reasonable expectation of success. Appellant argues that Examiner's rejection is predicated on an assumption that Scannon teaches a 240kD melanoma antigen that is a cell surface antigenic marker at a concentration in excess of that found in non-target sites. Appellant argues that Scannon does not discuss the location of the antigenic marker. Appellant argues that it was known in the art that an intracellular antigen can serve as a target for immunotoxin therapy and that at least

some 240K tumor antigens are intracellular in nature, thus one would not assume that Scannon teaches antigens on the cell surface (p. 7, section B). Appellant argues that the "gp240" antigen taught by Kirkwood is not necessarily the 240kD antigen of Scannon and that Scannon does not teach that the 240kD antigen is a glycoprotein. Appellant argues that Examiner offered no foundation for assessing that the claimed antigen appears to be the same as the prior art. Appellant argues that Examiner is only guessing that the antigenic markers are the same and has not met the burden of showing the antigen of the prior art and instant claims are identical or substantially identical (p. 8, section B).

The arguments have been considered previously and were not found persuasive for the reasons set forth in Section 3, p. 6-8 of the Final Office Action mailed 4/28/08, as summarized below. In response to Appellant's arguments, Examiner provided several references in addition to Kirkwood et al as evidence that the antibody conjugates taught by Scannon inherently bind the cell surface melanoma antigen recognized by antibody ZME-018. It is noted that Scannon refers to the antibody-RTA conjugates as "XMMME-001-RTA" or "XMMME-RTA-002" (see col. 5, lines 45-60; col. 6, lines 4-27; Table 1; col. 7, lines 31-51; Table II; all claims).

1) Ashcroft et al (Chem Commun, 2006, p. 3004-3006) provide evidence that ZME-018 antigen (to which ZME-018 antibody binds and recognizes) is also known as "gp240" and "high molecular weight melanoma-associated antigen (HMWMAA)" (p. 3004, col. 1).

2) Ferrone et al (J of Dermatology, December 1988, 457-465) provide evidence that HMWMAA (HMW-MAA) is a cell surface antigen (Table 1).

3) Martin et al (Human Gene Therapy, 1998, 9:737-746) provide evidence that XMMME-001-RTA binds HWAMAA. Martin et al teach that antibodies directed against HMWMAA have been used clinically to target toxic agents to melanomas and points to Oratz et al (below) as an immunoconjugate directed against HMWMAA.

4) Oratz et al (J Biol Response Mod, 1990, 9:345-354) as referred to by Martin et al (above), teach using XMMME-001-RTA immunoconjugate to treat patients with melanoma, hence XMMME-001-RTA, as referred to by Martin et al, is an immunoconjugate that binds HMWMAA (abstract, see entire paper). Further, Oratz et al teach that XMMME-001-RTA is the immunoconjugate described in US Patent 4,590,071, Scannon et al (p. 346, col. 2, reference #9).

Given the evidence above, it is clear that the antibody conjugate taught by Scannon inherently binds the cell surface antigen recognized by monoclonal antibody ZME-018, hence the issues remain the same.

Appellant argues that Examiner cited four references to demonstrate that "the antibody conjugates taught by Scannon inherently bind cell surface melanoma antigen recognized by antibody ZME-018," but one of the references is from 2006. Appellant argues that although inherency does not require recognition of a characteristic in the prior art, without such recognition, the combination of references in this case cannot be

said to show the required combination of known elements by known processes with no more than what would be expected at the time. Appellant argues that without the 2006 reference, Examiner makes no argument that a person of skill would believe the teachings of Scannon could be combined with the teaching of Kirkwood and Ferris and would be expected to result in "a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated or fused to the biological response modifier." Appellant argues that obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established (p. 8-9, Section B).

The arguments have been considered but are not found persuasive. It is noted, as clearly stated in the rejection, that Kirkwood et al was provided as *evidence* that the antibody conjugate taught in Scannon binds the same cell surface melanoma ZME-018 antigen claimed, hence binding the ZME-018 antigen is an inherent characteristic of the antibody conjugate taught by Scannon. Kirkwood et al and the four references cited (Ashcroft, Ferrone, Martin, and Oratz) as evidence provide sufficient evidence that the method of treating melanoma taught by Scannon obtains and administers an antibody conjugate that binds the same cell surface ZME-018 antigenic marker expressed at excess in melanoma compared to other non-target sites, as recited in the claims. Appellant has not shown that the 240kD melanoma antigen taught by Scannon is different from the ZME-018 cell surface antigen recited in the claims.

References available after the filing date that are provided as evidence to demonstrate an inherent property are acceptable. MPEP 2124 states: In certain

circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism.

The motivation to combine references is not based on Kirkwood or any reference provided as evidence to demonstrate the inherent property of the antibody conjugate taught by Scannon, therefore arguments drawn to the publication dates of the references provided as evidence are not persuasive. The cell surface location is an inherent property of the 240kD melanoma antigen taught by Scannon and antibody conjugates binding the antigen are taught by Scannon, therefore there is no unexpected result of antibody conjugates binding a cell surface antigen expressed at higher concentrations in melanoma than at other non-target sites, as Appellant appears to be arguing.

It is the combination of Scannon and Ferris that establishes a *prima facie* case of obviousness, for the reasons of record. Scannon provides motivation to target toxins to melanoma for therapy because of selective binding activity of the antibody for the melanoma-specific antigen 240kD. Ferris et al teach that conjugating antibodies to either ricin A toxin or the biological response modifier TNF are known for selectively delivering the toxin or TNF to tumor cells. One would have been motivated to use an antibody-TNF conjugate in the method of Scannon et al in order to selectively kill melanoma cells. One of ordinary skill in the art would have a reasonable expectation of success of using the antibody-TNF conjugate to treat melanoma in a human patient

because the antibody taught by Scannon et al successfully and specifically targets a toxin to human melanoma cells and TNF is a known cytotoxic agent for killing tumor cells.

Further, the function of the antibody- ricin A toxin conjugate taught by Scannon et al had a known function for treating melanoma by targeting the toxin to melanoma that expressed a target antigen that the antibody recognized. The TNF of the antibody-TNF conjugate taught by Ferris et al is known to exert cytotoxic effects on cancer cells. Given the known functions of the toxins and antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF for the ricin toxin), and the results of the substitution would have been predictable for treatment.

Appellant argues that Examiner failed to account for the limitation recited in the claims- the determination that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site. Appellant argues that the state of the prior art is to treat all subjects as if all were afflicted with the same or similar generic type of cancer, however the instant claims are drawn to treating a specific subpopulation of cancer patient that express a specific antigen and this limitation is not met by Examiner's citations (p. 9, section B).

The arguments have been considered but are not found persuasive. As stated in the rejection of record, Scannon teaches that melanoma tumor cells of melanoma patients express the 240kD antigen recognized and bound by the antibody-ricin A conjugate, therefore it was determined that cells of the melanoma patient's cancer

express the 240kD antigen recognized and bound by the antibody-ricin A conjugate. This claim limitation is taught in the prior art and the claims remain rejected under 35 U.S.C. 103(a) for the reasons of record.

(B) With regards to claim 16 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, **Scannon et al** and US Patent 4,771,128, **Ferris et al**, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of **Blick et al**, Appellant argues that claim 16 is not obvious for all the reasons described in section B of the Appeal Brief (p. 10, Section C).

The arguments have been considered but are not found persuasive for the reasons of record and set forth above.

Appellant argues that Examiner attempts to show obviousness of dependent claim 16 without the Kirkwood reference, even though Examiner felt the reference was necessary to reject independent claim 26 (p. 10, section C).

The argument has been considered but is not found persuasive. As stated above, the Kirkwood reference was provided as *evidence* to demonstrate the inherent properties of the 240kD antigen and antibody conjugate binding it. The rejection of claim 16 clearly incorporates the references and rejection as applied to independent claim 26 (as stated on the record): “Claim 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, **as**

applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of Blick et al (Cancer Research, 1987, 47:2986-2989)." Therefore the rejection applied to claim 26, also applies to claim 16.

Appellant argues that Examiner failed to show that (1) Blick teaches the 240kD antigen of Scannon and the antigen in the claims are the same antigen; and (2) the additional limitation that TNF is TNF-alpha as required in claim 16. Appellant argues that Blick does not relate to immunotoxins or similar targeted therapy, this a person of skill in the art reading Blick would have very little reason to believe that whatever "success" was reported therein could be repeated by a targeted TNF-alpha conjugate, particularly considering there is no evidence of record presented that such a conjugate would retain TNF activity. Appellant argues that a person of skill in the art at the time of filing would not be motivated to combine the references with a reasonable expectation of success (p. 10-11, section C).

The arguments have been considered but are not found persuasive because the elements of the rejection of claim 26 are incorporated into the rejection of claim 16, and Examiner did show the 240kD antigen taught by Scannon is the same antigen as claimed for the reasons of record. Examiner provided teachings in Scannon, Ferris, and Blick as to why substituting the generic TNF in the method taught by Scannon and Ferris with the TNF-alpha in the antibody-conjugate would be obvious, why one would be motivated and have a reasonable expectation of success. Cytokines, such as TNF, are known to have cytostatic and cytotoxic effects against a wide range of human tumor

cells, Blick teaches that TNF-alpha has antitumor effects in cancer patients, and Ferris teach that conjugating TNF to antibodies to target treatment of cancer cells is known and successful, hence, given the known functions of the cytokines and success of making antibody conjugates, one of skill in the art could have substituted one known element for another (the TNF-alpha for the generic TNF), and the results of the substitution would have been predictable. One would have been motivated to use the TNF-alpha as the TNF of the antibody conjugate in order to specifically kill tumor cells. Given the teaching of the combined references, one of skill in the art would have a reasonable expectation of success making an antibody-TNF-alpha conjugate and treating melanoma using the conjugate because methods of making TNF-antibody conjugates are known and their antitumor effects are known.

Appellant reiterates the argument that Examiner failed to account for the limitation recited in the claims- the determination that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site (p. 11, section C).

The argument has been considered but is not found persuasive because Scannon teaches this step as stated above. The claims remain rejected under 35 USC 103(a) for the reasons of record.

(C) With regards to claim 23 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, **Scannon et al** and US Patent 4,771,128,

Ferris et al, as applied to claims 7, 10, 13, 14, 24-29, and 32 above, and further in view of **Ghose et al**, Appellant argues that claim 23 is not obvious because the claim from which it depends is not obvious (*In re Fine*). Appellant argues that Examiner attempts to show obviousness without the Kirkwood reference and fails to show how Ghose teaches what Kirkwood was cited for and the limitations of claim 23. Appellant argues that Ghose only teaches that some antibodies may be fused to some biological response modifiers and does not address the deficiencies in Examiner's rejections. Appellant reiterates the argument that none of the references cited account for the determination that the patient's cancer express a certain antigen as describe in section A and B of the Appeal Brief (p. 11-12, section D).

The arguments have been considered but are not found persuasive. As stated above, the Kirkwood reference was provided as *evidence* to demonstrate the inherent properties of the 240kD antigen and antibody conjugate binding it. The rejection of claim 23 clearly incorporates the references and rejection as applied to independent claim 26 (as stated on the record): "Claim 23 remains rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, Scannon et al, filed 9/25/1984, issued 5/20/1986 and US Patent 4,771,128, Ferris et al, filed 10/10/1986, issued 9/13/1988, **as applied to claims 7, 10, 13, 14, 24-29, and 32 above**, and further in view of Ghose et al (Crit Rev Ther Drug Carrier Syst, 1987, 3:263-359)." Therefore the rejection applied to claim 26, also applies to claim 23.

Appellant admits that Ghose teaches antibodies can be fused to biological response modifiers. Substituting the antibody-biological response modifier conjugate

taught in the method of Scannon and Ferris with the fused immunoconjugate taught by Ghose is *prima facie* obvious for the reasons of record.

As stated above, Scannon teaches the step of determination that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site. The claims remain rejected under 35 USC 103(a) for the reasons of record.

(D) With regards to the rejection of claims 7, 24, 26-29, and 30 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,753,894, **Frankel et al**, in view of US Patent 4,771,128, **Ferris et al**, Appellant argues that Frankel and Ferris do not teach the claim limitations recited in claim 26. Appellant argues that the breast cancer of the prior art would not necessarily have been identified or diagnosed as a patient having a breast tumor and the patient's breast cancer would not necessarily be expressing the breast cancer antigen targeted by the antibody conjugate for killing tumor cells. Appellant argues that none of the antibodies presented in Frankel bind to all of the breast cancer cells or tissue sections tested in excess of that found at other non-cancerous sites (Frankel, Tables I-III), therefore, there are breast cancer cell lines, tissues, and tumors that do not express antigens to Frankel's antibodies. Appellant argues that the fact that a patient's cancer might express a given antigen but a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result characteristic (*In re Rijckaert*) (p. 5, section A).

The arguments have been considered but are not found persuasive for several reasons. First, Frankel teaches breast cancer cells and tissues express cell surface antigens that specific monoclonal antibodies bound to in excess to breast cancer as compared to other non-target sites, such as other normal tissues. For example, Table 2 identifies antibodies with a score of 1 or 2 that exhibit increased staining or binding to breast cancer tissue, wherein these antibodies have a score of zero, or no detectable binding in Table 1 to non-target sites such as normal tissues; hence patients with breast cancer identified in Table 2 as having an antibody binding at a score of 1 or 2, and a score of 0 in Table 1, would be identified as having a breast tumor comprising a cell surface antigenic marker at concentrations in excess of that found at other non-target sites. Further, Frankel (col. 5, lines 17-47) teaches methods of diagnosing (identifying) breast cancer patients using the antibodies. Although Frankel teaches there exist several different antigens expressed in excess in breast cancer compared to other non-target sites that are recognized by different antibodies, this teaching does not make the reference any less anticipatory for the instantly claimed method. MPEP 2123 states: "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Frankel identifies breast cancer from patients that *does express* a cell surface antigenic marker in excess of that found in non-target sites, hence the step of identifying a patient having a breast tumor with said antigenic marker is anticipated.

Second, Appellant is arguing limitations not recited in the claims. Appellant argues that none of the antibodies presented in Frankel bind to all of the breast cancer cells or tissues tested in excess of that found at other *non-cancerous sites*. The claims recite “non-target sites”, not "non-cancerous sites” hence, the antigenic marker can be expressed in breast cancer in excess compared to any non-target site, including *any* normal or cancerous tissue type not targeted, and in this case, a site that is not breast cancer.

Appellant argues that Examiner is incorrect stating: “given the breast cancer patients being treated with the immunoconjugates are identified as having breast cancer, the cells of the breast tumor in the patient would express an antigen recognized and bound by the antibodies in the immunoconjugates taught by Frankel.” Appellant points to breast cancer labeled R in Table 2 and argues that the only three antibodies that bind to R also bind significantly to normal tissues in Table 1. Appellant argues that in this case, the breast cancer does not express an antigen recognized by Frankel’s antibodies at higher concentrations than normal tissue. Appellant argues that Examiner relies on common knowledge to show inherent properties that Appellant has shown do not exist and Examiner failed to provide evidence (p. 5-6, section A).

The arguments have been considered but are not found persuasive for several reasons. First, Appellant appears to be arguing limitations not recited in the claims. As stated above, the claims recite that the antigenic marker can be expressed in breast cancer in excess compared to any *non-target site*, including *any* normal or cancerous

tissue type not targeted, and in this case, a site that is not breast cancer. Further, the claims only require the tumor comprise an antigen marker at concentrations *in excess* of that found at other non-target sites, and there is no level of significant expression required other than concentrations in excess. In Appellant's specific example R breast cancer, the three antibodies do recognize and bind an antigen on the breast cancer at concentrations in excess compared to those found at other non-target sites. For example antibodies 2G3, 245E7, and 280D11 all bind breast cancer R at a score of 2, 2, and 1, respectively in Table 2. All three antibodies fail to bind the non-target sites of brain, heart, and ovary, with a score of zero in Table 1. Contrary to Appellant's arguments, the patient with breast tumor R is identified as having a tumor with cells comprising a cell surface antigenic marker at concentrations in excess of that found at other non-target sites, as required by the claims. It is also noted that a binding score of 2 would be considered a concentration in excess of a binding score of 1.

Second, as stated above, although Frankel teaches there exist several different antigens expressed in excess in breast cancer compared to other non-target sites that are recognized by different antibodies, this teaching does not make the reference any less anticipatory for the instantly claimed method. MPEP 2123 states: "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Frankel identifies breast cancer from patients that *does express* a cell surface antigenic marker in excess of that found in non-target

sites, hence the step of identifying a patient having a breast tumor expressing said antigenic marker is anticipated.

Appellant argues that Examiner fails to take into account the teachings of Frankel as a whole. Appellant argues that Frankel teaches treating any patient with breast cancer regardless of whether or not they express the specific antigen. Appellant argues that the limitation of the instant claims, that a determination be made that the patient's cancer expresses the targeted antigen, has not been accounted for by Frankel and would not have been obvious to one of skill in the art given the disclosure of Frankel. Appellant argues that Ferris does not address the deficiencies of Examiner's rejection described above and does not account for determining if a patient's tumor expresses a certain antigen (p. 6-7, section A).

The arguments have been considered and are not found persuasive. Examiner did consider the teaching of Frankel as a whole, and Frankel clearly states in the abstract that monoclonal antibodies were characterized to selectively bind human breast cancer and conjugated to a toxin for treating human breast cancer. Frankel teaches using the antibodies to diagnose breast cancer and for targeting of drugs to specific antigens expressed on breast cancer. As stated in the rejection of record and above, Frankel did determine that the breast tumor cells of a breast tumor patient express an antigen recognized by an antibody (Table 2) and the antibody is

administered as a toxic conjugate for treatment. The claimed invention is obvious over the combined references for the reasons of record.

(E) With regards to claims 7, 24, 26-29, 31 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,666,845, **Mattes et al**, in view of US Patent 4,771,128, **Ferris et al**, Appellant argues that no reference in the record has been cited that accounts of targeting cervical cancer. Appellant argues that Examiner cites antibody MH94 but Appellant states there is no reference to MH49 in Mattes. Appellant argues that MH94 is not expressed on human cervical carcinoma cells at concentration in excess of that found in other tissues. Appellant argues that in Table I of Mattes, monoclonal antibody MH94 binds weakly to cervical carcinoma cells ME180 and Table II shows that MH94 binds to normal pancreas, ureter, breast, prostate cervix, urinary… sebaceous gland. Table II shows that MH94 binds to normal fetal stomach tissue, intestine, pancreas…cervix epithelial cells. Appellant argues that MH94 binds to normal cell types. Appellant argues that an antigen MH94 binds only weakly to cervical carcinoma cell lines, but also binds an excess of normal adult and fetal tissues. Appellant argues that the limitation that the cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites of the instant claims has not been met (p. 12-13, section D).

The arguments have been considered but are not found persuasive. It is noted that Examiner inadvertently switched the 4 and 9 of MH94 but it is readily apparent from

Table I and II and column 11 which antibody Examiner was referring to, especially given Appellant's arguments identifying the antigen/antibody. Contrary to Appellant's arguments, antigen MH94 is expressed at concentrations in excess in cervical cancer compared to that found at other non-target sites. It is noted that the monoclonal antibodies binding to the identified antigens share the same name as the antigen, therefore antibody MH94 binds cell surface antigen MH94 (col. 11, lines 55-61, MH94 antigen; col. 14, lines 45-63, MH94 antibody). Table I demonstrates that mAb MH94 binds cervical carcinoma at a score of 1 compared to other non-target sites with a score of zero, as required by the claims. Further, Table 2 in the footnotes, indicates that of the 27 normal tissues and 24 normal fetal tissues tested for antigen presence using antibody MH94, those tissues not listed in Table II were negative for binding, hence antigen MH94 is found in excess on cervical carcinoma compared to the non-target tissues not listed in Table II.

Again, Appellant is arguing limitations not recited in the claims. Appellant appears to be arguing that the antigenic marker (MH94) cannot be expressed in any other tissues or at any level in any other tissues outside of cervical carcinoma. However, the claims are drawn to identifying a patient having a tumor, which tumor comprises cells for targeting and *wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites*. Non-target sites can include any normal or cancerous tissue that is not being targeted, and in this case, cervical carcinoma is being targeted, so all other tissues can be non-target sites. Further, an antibody binding score of 1 is still greater than a score of zero, wherein the

binding score of 1 for a tissue identifies an antigen present in excess compared to a tissue with a binding score of zero. Although antibody MH94 bound to some normal tissues, this data does not make the reference any less anticipatory because the MH94 antigen is still expressed at concentrations in excess in cervical carcinoma of that found at other non-target sites as indicated in Tables I and II and as required by the claims.

Appellant argues that mAb MH94 binds "weakly" to cervical carcinoma cell line, however, the strength of antibody binding to MH94 is not known or relevant to the instant rejection. Further, Table I does not indicate the strength of antibody binding, but rather provides a staining score indicating the amount of binding or the amount of antigen present in the tissue being stained with antibody (see Table 1 footnote). Table 1 clearly shows that antigen MH94 is present in excess in cervical carcinoma (score of 1) compared to other non-target sites with a score of zero, as required by the claims. Table 2 indicates that of the 27 normal tissues and 24 normal fetal tissues tested for antigen presence using antibody MH94, those tissues not listed in Table II were negative for binding, hence antigen MH94 is found in excess on cervical carcinoma compared to the non-target tissues not listed in Table II, as required by the claims. Given the data shown in Tables I and II, Mattes identified cervical carcinoma from a patient that expresses MH94 antigen at concentrations in excess of that found at other non-target sites, hence identified a patient having said carcinoma.

Appellant argues that Examiner argues that all cervical cancers will express the antigen MH94 but Mattes only tested one line. Appellant argues that Mattes does not disclose detecting each patient for the antigen prior to treatment, thus the limitation that each patient is tested for expression of the antigen has not been met (p. 13, section D).

The arguments have been considered but are not found persuasive. Mattes identified cervical carcinoma from a patient that expresses MH94 antigen at concentrations in excess of that found at other non-target sites, hence identified a patient having said carcinoma and determined the patient's cancer expressed MH94 antigen recognized and bound by MH94 antibody, as required by the claims. Further, as stated in the previous Final Office Action, sections 11 and 12, Mattes disclosed methods of diagnoses (i.e. identifying a patient with cervical carcinoma that expresses the antigen bound by MH94) using the monoclonal antibody (MH94) tagged with a radioactive label for localizing cervical carcinoma in a patient (col. 13, lines 54 through col. 14, line 26). The fact that Mattes tested one cervical carcinoma line does not make the reference any less anticipatory. Mattes in combination with Ferris teach all the limitations of the claims and the claims remain rejected under 35 USC 103(a) for the reasons of record.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Laura B Goddard/

Examiner, Art Unit 1642

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/Larry R. Helms/

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